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(54) Title: RECOMBINANT FACTOR VIII HAVING INCREASED SPECIFIC ACTIVITY

(57) Abstract: The present invention relates to recombinant factor VIII having a specific activity that is higher than that of the corresponding wild-type factor VIII. The present invention also relates to methods of making and using the recombinant factor VIII. The present invention also relates to an isolated nucleic acid molecule that encodes the recombinant factor VIII, as well as DNA expression systems and host cells containing the isolated nucleic acid molecule.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/40234

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 35/14, 35/16, 38/00; C07K 1/00, 14/00; C12N 15/63, 15/85
US CL : 530/380, 383; 435/69.1, 69.6, 320.1, 325; 5142, 802, 834; 536/23.1; 930/100

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 530/380, 383; 435/69.1, 69.6, 320.1, 325; 5142, 802, 834; 536/23.1; 930/100

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WAKABAYASHI et al. Residues 110-126 in the Factor VIII Heavy Chain Contain a Ca ²⁺ Binding Site Required for Cofactor Activity. Blood, November 16, 2003, Vol. 102, No. 11, p. 542a, abstract 1988.	1-10, 13, 23-26, 32-42, 47
Y		1-11, 13-14, 16, 18-27, 29, 31-52
Y	US 5,859,204 A (LOLLAR) 12 January 1999 (12.01.99), abstract, columns 2-4, Col. 33, Table III, Col. 34, Table IV, Col. 40, Table V.	11, 19-22, and 48-52
Y	AMANO et al. Mutation at either Arg336 or Arg562 in Factor VIII is Insufficient for complete resistance to Activated Protein C (APC)-mediated inactivation: Implications for the APC resistance test. Thromb. Haemost. 1998, Vol. 79, pp. 557-563, especially abstract, p. 559, section bridging columns).	14, 27
Y	SWAROOP et al. Mutagenesis of Potential Immunoglobulin-binding Protein-binding site Enhances Secretion of Coagulation Factor VIII. J. Biol. Chem. 1997, Vol. 272, No. 39, pp. 24121-24124, especially abstract, p. 21123, fig. 1.	16, 29
Y, P	US 6,759,216 B1 (LOLLAR) 06 July 2004 (06.07.04), abstract, Col. 2, lines 54-67).	18, 31



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"T "	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"O " document referring to an oral disclosure, use, exhibition or other means		
"P " document published prior to the international filing date but later than the priority date claimed		

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International application No.
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C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	WAKABAYAH I et al. Factor VIII:E113A Represents a High Specific Activity Factor VIII arising from a Single Point Mutation within the Ca2+ Binding Site. Blood, November 2004, Vol. 104, No. 11, p. 479a, abstract 1725.	1, 2, 3, 4, 5, 7, 8, 9, 10, 12, 13
X, P --- Y, P	WAKABAYASHI et al. Residues 110-126 in the A1 domain of Factor VIII Contain a Ca2+ Binding Site Required for Cofactor Activity. J. Biol. Chem. March 2004, Vol. 279, No. 13, pp. 12677-12684.	1-10, 13, 23-26, 32- 42, and 47 1-11, 13-14, 16, 18- 27, 29, 31-52
A	SARAFANOV et al. Cell Surface Heparan Sulfate Proteoglycans Participate in Factor VIII Catabolism Mediated by Low Density Lipoprotein Receptor-related Protein. J. Biol. Chem. April 2001, Vol. 276, No. 15, pp. 11970-11979.	12, 17, 30
A	LENTING et al. The sequence of Glu1811-Lys1818 of Human Blood Coagulation Factor VIII Comprises a Binding Site for Activated Factor IX. J. Biol. Chem. January 1996, Vol. 271, No. 4, pp. 1935-1940.	15 and 28

INTERNATIONAL SEARCH REPORT

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PCT/US04/40234

Continuation of B. FIELDS SEARCHED Item 3:
STN (Bioscience), EAST (all databases), sequence search, search terms: rfviii, factor viii, fviii, calcium binding, A1,
Mn2+, Ca2+, hybrid, chimeric, inactivation cleavage site, factor IX binding, secretion, glycosylation recognition sequence.